REMARKS/ARGUMENTS

This amendment is in response to an Office Communication mailed on June 18, 2003 asserting that the response filed on March 18, 2003 was not in compliance with voluntary revised amendment practice. Applicants have amended the claim listing to indicate that claims 1-9 are cancelled. Applicants assert that this response is now in compliance with voluntary amendment practice. The following remarks are identical to those of the previously filed response.

With this amendment, Claims 10-17, 20 and 21 are pending. Claims 10-14 are cancelled without prejudice to subsequent revival. Claims 17, 20 and 21 are withdrawn by the Examiner as allegedly being outside the scope of the originally elected invention. Applicants respectfully traverse this withdrawal. Claims 15 and 16 are rejected. For convenience, the Examiner's rejections are addressed in the order presented in the December 18, 2002 Office Action.

I. Status of the Claims

Claims 15 and 16 are currently under examination and are rejected. Applicants also traverse the restriction requirement imposed by the Examiner and assert that claims 17, 20 and 21, which depend on claim 15, should also be under examination.

Claim 17 has been amended to recite that the candidate bioactive agent is a member of a library of candidate bioactive agents and the cell is a member of a plurality of cells. Support for this amendment is found, for example, at page 3, lines 22-24 and page 24 line 18 through page 25, line 7. This amendment adds no new matter.

Claim 20 has been amended to recite further comprising determining the acitivty of the R0101 protein in the presence of the candidate bioactive agent. Support for this amendment is found, for example, at page 3, lines 19-22. This amendment adds no new matter.

II. Election/Restriction

The Examiner alleges that claims 17, 20, and 21 are directed to inventions that are independent or distinct from the originally claimed invention, *i.e.*, Group I, and has thus restricted claims 17, 20, and 21 and withdrawn them from prosecution. Applicants respectfully traverse the restriction.

Elected Group I is directed to a method of screening for a bioactive agent that is capable of binding to cell cycle protein R0101 and is represented by claims 15 and 16, currently under examination. In order for claimed inventions to be independent, the inventions must not be connected in design, operation, or effect under the disclosure of the application under consideration. MPEP 802.01. In order for claimed inventions to be distinct, the inventions must not be patentable over each other. MPEP 802.01.

The Office Action asserts that claims 17, 20 and 21 are "outside the limitations of Claims 15 and 16" (page 2). Applicants point out that each of Claims 17, 20 and 21 depend from Claim 15, thereby comprising all of the limitations of this independent claim. Claim 15 describes a method comprising 2 steps; the "comprising" provides that any procedure having these two steps, regardless of how many other steps are involved, is encompassed by this claim. Therefore, claims 17, 20 and 21 cannot be outside the limitations of Claim 15.

The Office Action alleges that claim 17 is drawn to a method comprising steps that are not required to screening for a bioactive agent that binds to cell cycle protein R0101, essentially the subject matter of elected Group I. Applicants respectfully point out that claim 17, like claim 16, depends on claim 15 and is directed to the method of claim 15 done using multiple bioactive agents (*i.e.*, a library of bioactive agents) at the same time. Thus, claim 17 and claims 15 and 16 share design, operation, and effect and are not independent.

The Office Action alleges that claim 20 is outside the scope if the elected group and thus is separate and distinct from claims 15 and 16. Applicants respectfully

point out that claim 20, like claim 16, depends on claim 15 and is directed to the method of method of claim 15 done with the additional step of determining the activity of R0101 in the presence of a candidate bioactive agent. One of the activities of the claimed cell cycle protein is binding to PCNA. (Specification at page 31, lines 11-15.) A functional binding relationship between R0101 and PCNA is a limitation of claim 15. Thus, the differences in design between the claims are negligible and claims 15 and 20 have the same operation and effect, *i.e.*, determining binding of the bioactive agent to the cell cycle protein R0101.

The Office Action alleges that claim 21 is outside the scope if the elected group and thus is separate and distinct from claims 15 and 16. The Office Action further alleges that claim 21 reads on a method of making a composition *per se*. Applicants respectfully traverse and remind the Examiner that a dependent claim is construed to include all the limitations of the claim incorporated by reference into the dependent claim. Applicants respectfully point out that claim 21, like claim 16, depends on claim 15 and is thus also directed to a method for screening a bioactive agent capable of binding to the cell cycle protein R0101. There is no limitation in claim 21 to suggest that a method of making a composition is being claimed. Claim 21 is directed to the method of claim 15 done in the presence of PCNA. A functional binding relationship between R0101 and PCNA is a limitation of claim 15. Thus, the differences in design between the claims are negligible and claims 15 and 21 have the same operation and effect, *i.e.*, determining binding of the bioactive agent to the cell cycle protein R0101.

If Claim 15 is patentable, claims 17, 20 and 21 are necessarily also patentable. However, since claims 17, 20 and 21 are species of claim 15, claim 15 cannot be patentable over any of claims 17, 20 and 21. Furthermore, as discussed above, the examined and excluded claims are connected in connected in design, operation, and effect because they necessarily comprise identical steps. Claims 17, 20 and 21 are not independent and distinct from claim 15 and the exclusion of claims 17, 20 and 20 from

prosecution in the present case is inconsistent with the rules set forth in MPEP 802.01. Therefore, Applicants respectfully request inclusion of claims 17, 20 and 21 in the prosecution of the present application.

III. Information Disclosure Statement

According to the Examiner, the original IDS filed on June 2, 2002 fails to comply with 37 C.F.R. 1.98(a)(2) because the statement and the appended references are illegible. Applicants enclose new copies of the IDS and submitted references and respectfully request that the Examiner consider them.

IV. Rejection under 35 U.S.C. §101

Claims 15 and 16 are rejected under 35 U.S.C. §101 for allegedly lacking specific, substantial, or credible utility. Applicants respectfully traverse.

The essential basis of this rejection is the assertion that the protein R0101, as described in the present specification is "an "orphan protein" . . . whose cDNA has been isolated because of its similarity to known proteins." (page 4 of the Office Action) Applicants respectfully remind the Examiner that the specification must be taken as a whole for what it teaches. While the specification does show certain sequence similarities to other proteins (e.g., Fig. 2B), this is far from the extent of characterization of biological significance of R0101 provided. For example, R0101 is shown to be overexpressed in cancer tissue as compared to normal tissue (Fig. 5). R0101 is localized in the nucleus (Fig. 4). R0101 binds PCNA (Figs. 6, 7 and 8;), a well-known cell cycle modulating protein (*see*, e.g., Kelman, Oncogene 14:629-640 (1997), submitted as Exhibit A with Applicants' response filed 9/10/01) and such binding is dependent on an identified region of the r0101 protein (Figs. 7 and 8). And, R0101 competes for binding to PCNA with p21 (Figs. 6 and 8), also a well known cell cycle modulating protein whose cell cycle modulating activity is known to involve interacting with PCNA (*see*,

e.g., Kelman, page 637, first full paragraph). Applicants reiterate that the Kelman reference is only provided as an example of what was of general knowledge in the art.

Unfortunately, the above facts are in direct contradiction to statements made in the Office Action. For example, "neither the specification nor the art of record identifies even a single disease or disorder that has been shown to be associated with cell cycle protein R0101". (page 5) In fact, the present specification shows to one of ordinary skill in the art that R0101 is associated with breast cancer, uterine cancer, cervical cancer, brain cancer, kidney cancer, liver cancer, lung cancer, esophageal cancer and rectal cancer (Fig. 5). The Office Action also asserts that ". . . the cell cycle protein R0101 of the instant invention has not been shown to be associated with a particular physiological process that an artisan would wish to manipulate for assaying bioactive agents for identification of compounds which bind thereto." (page 6) In fact, overexpression of R0101 in the various cancers described above make this an obvious target for identifying agents that bind thereto for diagnostic purposes. R0101's interference with the known binding of PCNA and p21 provides another obvious reason for the presently claimed screens. Furthermore, the overexpression in cancers, localization to the nucleus and interaction with PCNA and p21 disclosed in the present specification provides ample suggestion to the skilled artisan that R0101 is directly involved cell cycle regulation. Applicants submit that the present specification should be considered as a whole with regard to the utility of the claimed invention, as further described below.

The Applicants assert that the present invention, methods for screening for a bioactive agent capable of binding to the cell cycle protein R0101, has utility. Applicants bring to the Examiner's attention evidence within the specification that R0101 expression is increased in certain cancers. The claimed screening methods have utility because they make possible the routine identification of bioactive agents that bind to R0101 protein, *i.e.*, for the diagnosis of, or prognostic evaluation of cancer. With this

amendment, Applicants include an expert declaration under 37 C.F.R. § 1.132 by Dr. Yasumichi Hitoshi explaining that one of skill in the art would recognize the utility of the invention claimed in the present application. In addition Applicants attach a peer-reviewed publication by the inventors describing the use of R0101 as a prognostic or diagnostic indicator of certain cancers. (Exhibit A, Yu, *et al.*, *Oncogene* 20:484-489 (2001)).

A. Introduction

According to the MPEP, in order to assess utility, the Examiner should review the specification to determine if there are any statements asserting that the claimed invention is useful for any particular purpose. An invention has utility if the utility is specific, substantial and credible. A utility is specific if it is specific to the subject matter claimed. A utility is substantial if it has a real-world use. A utility is credible if it would be believable to one of skill in the art. In most cases, an applicant's assertion of utility creates a presumption of utility that is sufficient to satisfy the utility requirement of 35 U.S.C. § 101.

With regard to utility of inventions with pharmacological utility, ". . . a disclosure that identifies a particular biological activity of a compound and explains how that activity can be utilized in a particular therapeutic application of the compound does contain an assertion of specific and substantial utility for the invention." MPEP 2107.02IIA. In addition, ". . .evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility." MPEP 2107.03I, *citing Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985). For molecules that have a demonstrated utility for diagnosis or prognosis of a particular disease, methods to identify materials useful to diagnose the disease, (*e.g.*, materials that bind to

the molecule), also have utility. See *e.g.*, Revised Interim Utility Guideline Training Materials, Example 12, page 69-70.

A *prima facie* showing of lack of utility by the Examiner must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The present application claims methods for screening for a bioactive agent capable of binding to the cell cycle protein R0101. After reading the application, the skilled practitioner would appreciate that R0101 modulates known cell cycle proteins and has increased expression in certain cancers. In addition, the skilled practitioner would (1) know how to routinely identify bioactive agents that bind to R0101 using the claimed methods, and (2) understand that bioactive agents that bind to R0101 are useful for diagnostic and prognostic tests for certain cancers.

B. Examiner's rejections

In the December 18, 2002 Office Action, the Examiner alleges that the instant specification fails to describe the practical utility of the claimed invention. According to the Examiner, there is no evidence showing that the R0101 protein has a biological role or what that role might be. Specifically, the Examiner alleges that neither the specification nor the art of record shows that cell cycle protein R101 is associated with a single disease or disorder. In addition, the Examiner alleges that Applicants have not presented evidence of natural ligands or biological significance of the R0101 protein and therefore there is no patentable use for the protein.

Applicants respectfully traverse. The specification provides both an association between R0101 and cancer and natural ligand for the protein. In addition, In a Declaration under 37 C.F.R. § 1.132, submitted herewith, Dr. Yasumichi Hitoshi explains that the R0101 protein has a physiological role and function, and is overexpressed and therefore, associated with specific cancers. The R0101 protein binds

to the PCNA protein, which has a well-established function in DNA synthesis. The R0101 protein is also overexpressed in specific cancers (see attached declaration and Figure 5 of the specification). Furthermore, Dr. Hitoshi explains that because the R0101 protein has the asserted association with specific cancers, methods to identify bioactive agents that bind to R0101 are useful. According to Dr. Hitoshi, bioactive agents that bind to R0101 are useful for diagnosis and prognostic evaluation of specific cancers.

Applicants, therefore, submit that the methods have a specific, substantial and credible utility.

C. R0101 is a cell cycle protein that has increased expression in certain cancers and is associated with certain cancers.

In the Office Action the Examiner alleges that neither the specification nor the art of record shows that cell cycle protein R0101 is associated with a single disease or disorder. Applicants respectfully traverse the allegation and assert that the specification as filed discloses an association between cell cycle protein R0101 and the disease cancer. Figure 5 of the application shows that R0101 exhibits elevated expression in certain cancers relative to non-cancer cells from the same tissues, *e.g.*, esophageal cancer, breast cancer, uterine cancer, cervical cancer, brain cancer, kidney cancer, and lung cancer. The attached declaration of Dr. Hitoshi demonstrates that the skilled practitioner, after reading the present specification, including Figure 5, would believe increased levels of R0101 are associated with certain cancers, *e.g.*, esophageal cancer, breast cancer, uterine cancer, cervical cancer, brain cancer, kidney cancer, and lung cancer. In addition Applicants attach a peer-reviewed publication by the inventors describing the use of R0101 as a prognostic or diagnostic indicator of certain cancers. (Exhibit A, Yu, *et al.*, *Oncogene* 20:484-489 (2001)).

D. The physiological role of R101 is to bind to PCNA protein.

In the Office Action the Examiner alleges that Applicants have not presented evidence of natural ligands of R0101. Applicants respectfully traverse the allegation and assert that the specification as filed discloses that the PCNA protein, which has a well-known role in DNA synthesis, is a ligand for cell cycle protein R0101. Figure 6 shows that R0101 binds to PCNA in cells and moreover, that R0101 competes with p21 for binding to PCNA. P21 is another protein with a recognized role in the cell cycle and an association with certain cancers. R0101 binding to PCNA occurs through a conserved PCNA binding domain. (See, *e.g.*, figure 2b, p15PAF and R0101 are used interchangeably and refer to the same protein.) In addition, the R0101 binding to PCNA is specific and can be eliminated by specific mutations of the R0101 protein. (See, *e.g.*, Figure 7.) The attached declaration of Dr. Hitoshi demonstrates that the skilled practitioner, after reading the present specification, including Figures 2, 6, and 7, would believe that cell cycle protein R0101 binds to PCNA, a known DNA synthesis protein.

E. Because cell cycle protein R0101 has utilty, methods to identify bioactive agent that bind to R0101 also have utility.

Because of the overexpression of R0101 in certain cancers, one of skill in the art would recognize that bioactive agents that bind to R0101 are useful. For example, one of skill in the art would expect that bioactive agents that bind to a protein known to be overexpressed in certain cancers, as is R0101, would be useful as an indicator of the level of the protein and therefore as a diagnostic or prognostic indicator of those cancers. The declaration by Dr. Yasumichi Hitoshi explains that one of skill in the art would recognize that bioactive agents that bind to R0101 are useful as a diagnostic or prognostic indicator of certain cancers.

F. After reading the present application, the skilled practitioner would know how to identify bioactive agents that bind to R0101.

Methods to determine molecules that bind to a protein are known to those of skill in the art. Applicants have isolated a nucleic acid that encodes the R0101 protein and provide both the nucleic acid (*i.e.*, SEQ ID NO:1) and the encoded amino acid (*i.e.*, SEQ ID NO:2.) Applicants also provide description of bioactive agents at page 23, line 33 through page 27, line 26. Applicants further provide methods determine binding to R0101 and to screen for bioactive agents that bind to R0101 at page 27, line 31 through page 31, line 32.

G. Identification of bioactive agents that bind to R0101 is useful for modulating cell proliferation and for identifying new targets for diagnosis and treatment of cancer.

There are many instances where binding of an agent to a particular protein is useful for diagnosis, determination of prognosis, or treatment of cancer even though the protein itself may not cause cancer. Bioactive agents that bind to proteins that are overexpressed in certain cancers can be used to diagnose the cancer or provide prognostic information about the disease, without a direct connection to the cause of the disease. For example, p21, a tumor suppressor, is overexpressed in some esophageal cancers and serves as a prognostic indicator of increased patient survival. (See Natsugoe *et al.*, *Clinical Cancer Research*, 5:2445-2449 (September, 1999), attached as Exhibit B). Also, prostate specific antigen (PSA) serves a as useful diagnostic indicator for prostate cancer, even though a direct causal relationship between expression of the protein and the disease ha not been shown. Thus, providing a prognostic or diagnostic test for a particular cancer is useful, even if the original cause of the cancer is unrelated to the protein targeted for diagnostic or prognostic information. Similarly, it is perfectly reasonable to expect that the identification of bioactive agents that bind to R0101, a cell cycle protein that is highly

expressed in some cancers, is an appropriate strategy to identify specific diagnostic or prognostic tools for certain cancers.

H. The demonstration that R0101 is overexpressed in certain cancers, coupled with methods for identifying bioactive agents that bind to R0101 and the level of skill in the art is sufficient to provide specific, substantial and credible utility for the claimed methods.

Applicants maintain that the demonstration that the R0101 is overexpressed in certain cancers, coupled with the methods disclosed in the specification and the level of skill in the art of ion channels, is sufficient to demonstrate specific, substantial and credible utility.

Specific utility

Applicants assert that the present invention has a specific utility. Specific utility is defined by the MPEP as a utility that is specific to the subject matter claimed. The MPEP explains that applications show sufficient specific utility when applicants disclose a "specific biological activity" and reasonably correlate that activity to a "disease condition." MPEP 2107.01, 2107.02. In this application, Applicant disclose a "disease condition", *i.e.*, esophageal cancer, breast cancer, uterine cancer, cervical cancer, brain cancer, kidney cancer, and lung cancer, that correlate with a increased expression of R0101. This application also demonstrates that R0101 binds to PCNA, a known cancer associated protein. This application provides methods of identifying bioactive agents that bind to R0101 for use as a diagnostic or prognostic indicator of the disease. Applicants therefore submit that the present invention has a specific utility, *e.g.*, identification of bioactive agents that bind to R0101 protein for diagnosis or prognostic evaluation of cancer.

Substantial utility

Applicants also assert that the present invention has a substantial or "real world" use. This application provides nucleic acids that encode R0101 protein. The application also demonstrates that R0101 is overexpressed in specific cancers. This application therefore has real world use in the cancer diagnosis and evaluation of prognosis. Throughout the specification, Applicants teach how to identify bioactive agents that bind to R0101 and how to use the bioactive agents. Applicants therefore submit that the present invention has a substantial utility, *e.g.*, the identification of bioactive agents that bind to R0101, useful for diagnostic or prognostic testing of specific cancers.

Credible utility

Finally, Applicants assert that the present invention has a credible utility. According to the MPEP, when an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office Personnel as being "wrong," even when there is reason to believe that the assertion is not entirely accurate. Rather Office Personnel must determine if the assertion of utility is credible, (*i.e.*, whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided) MPEP 2107.02 III B. Applicants submit that one of skill in the art after reading this application would (a) know how to identify bioactive agents that bind to R0101 (b) know how to use those bioactive agents that bind to R0101 for diagnostic or prognostic evaluation of specific cancers.

Accordingly, The Applicant respectfully requests that the utility rejection under 35 U.S.C. § 101 be withdrawn.

V. Rejection Under 35 U.S.C. §112, First Paragraph, Enablement

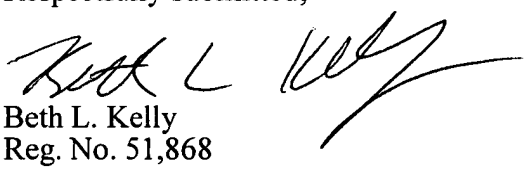
Claims 15 and 16 are rejected as not being enabled since the invention is allegedly not supported by either a clear asserted utility or a well established utility.

Applicants respectfully traverse the rejection. As described above, the invention claimed in the present application is supported by a specific, substantial, and credible utility. The Office Action also asserts that there is no known activity corresponding with R0101. Applicants traverse the rejection and reiterate that the specification provides an activity for R0101 in binding to PCNA. In addition, the application discloses an association between R0101 and specific cancers. Finally, the specification provides methods of identifying the bioactive agents that bind to R0101 and methods of using those agents. (See, *e.g.*, specification at page 27, line 31 through page 31, line 32, page 40 line 19 through page 53, line 23, and particularly page 41, lines 21-28. Accordingly, Applicants request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 415-576-0200.

Respectfully submitted,



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